Remarks

Status of the Claims

Pending claims

Claims 1 to 52 are pending.

Restriction Requirement and Election

In the Restriction Requirement dated November 8, 1999, the pending claims were restricted into four Groups. Claims of Group I (claims 1 to 19), Group II (claims 20 to 22) and Group IV (claims 43 to 52) were examined (the Examiner reconsidered and rejoined Groups I, II and III).

A divisional application (USSN 09/839,821) with claims directed to Group III, drawn to methods of using a functional site descriptor, has been filed and is co-pending.

Claims under examination, amended, canceled and added

Claims 1 to 22 and 43 to 52 are pending and under examination. Claims 1 to 5, 8 to 22, and 53 to 52 are pending as filed, claims 6 and 7 were amended in Applicants' response dated November 30, 2000 (submitted as a CPA preliminary amendment and response to the office action dated April 13, 2000). Claims 23 to 42, previously withdrawn from consideration as being drawn to a non-elected invention, are canceled in the instant amendment, without prejudice. In the instant amendment, claim 1, 15, 21 and 43 are canceled (in addition to previously withdrawn claims 23 to 42), claims 2 to 14, 16 to 20 and 44 to 52 are amended and claims 53 to 60 are added. Thus, after entry of the instant amendment, claims 2 to 14, 16 to 20, 22 and 44 to 60 will be pending and under consideration.

Notwithstanding the foregoing, Applicants respectfully submit that the amendments herein are being made to present Applicants' pioneering invention using preferred language and in a format requested by the Examiner for ease of examination, and not for purposes of patentability.

Outstanding Rejections

Claims 1 to 22 were rejected under 35 U.S.C. §101. Claims 1 to 22 and 43 to 52 were rejected under 35 USC §112, second paragraph. Claims 1, 3 to 10, 12, 15 to 22 and 43 to

50 were rejected under 35 USC §102(b) as allegedly anticipated by Holm, et al. (1997) PROTEINS: Structure, Function and Genetics 28:72-82. Claims 1 to 22 and 43 to 52 were rejected under 35 USC §103(a) as allegedly unpatentable over Wallace, et al. (1996) Protein Science 5:1001-1013. Applicants respectfully traverse all outstanding objections to the specification and rejections of the claims.

Interview with Examiner

Applicants thank the Examiner for the very helpful and courteous interview on April 4, 2001, with Gregory Einhorn, Esq., co-inventor Jacquelyn S. Fetrow, Ph.D., and Dan Chambers, Esq., representing the licensee, GeneFormatics, Inc., participating. Applicants also thank the Examiner for preparing the Interview Summary.

Support for the Claim Amendments

The specification sets forth an extensive description of Applicants' pioneering invention. Support for claims wherein a functional site descriptor comprises an amino acid residue identity constraint for at least one amino acid residue of the functional site can be found, inter alia, on page 23, lines 18 to 23. Support for claims wherein a functional site descriptor comprises one or more geometric constraints between at least three different atoms (coordinates in three dimensions) can be found, inter alia, on page 19, lines 14 to 21; page 24, lines 8 to 15, and Figure 6, including brief description of Fig. 6 on page 29, lines 18 to 29), page 31, lines 30 to 34. Support for claims wherein a functional site descriptor comprises one or more geometric constraints between at least three different amino acids can be found, inter alia, on page 35, lines 27 to 33. Support for claims wherein one or more geometric constraints of the functional site descriptor comprises an atom selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, a backbone pseudoatom and a beta-carbon can be found, inter alia, on page 23, lines 23 to 31. Support for claims directed to the methods of the invention as computer-implemented methods, as computer program products and computer systems can be found, inter alia, on pages 61 to 80.

Informalities

Sequence Rules

A paper copy of sequences and computer readable form placing the application in compliance with 37 C.F.R. §1.821(a)(1) and (a)(2) was filed November 30, 2000. As the Examiner had not received these documents as of the mailing of the instant office action, a copy of this response is attached, including a copy of the date-stamped post card confirming receipt by the USPTO.

Issues under 35 U.S.C. §101

Claims 1 to 22 stand rejected under 35 U.S.C. §101, because the claimed invention is allegedly directed to non-statutory subject matter. Specifically, it is alleged that claims drawn to "functional site descriptors" and libraries of these descriptors are non-statutory subject matter. Applicants respectfully disagree; however, to advance prosecution of this important invention, alternative language has been used.

After entry of the instant amendment, the claimed invention is drawn to computer program products, computer-implemented methods and computer systems comprising the computer program products. Applicants respectfully aver that computer program products, computer-implemented methods and computer systems are statutory subject matter under 35 U.S.C. §101.

For example, regarding computer-implemented methods, the following claim recently issued in United States Patent No. 6,242,180, entitled "Computer-aided visualization and analysis system for sequence evaluation," issued June 5, 2001:

1. **A computer implemented method** of calling unknown bases in a sample nucleic acid sequence, comprising:

inputting a plurality of probe intensities, each probe intensity indicating hybridization affinity between a nucleic acid probe and the sample nucleic acid sequence;

calling bases of the sample nucleic acid sequence according to the plurality of probe intensities;

identifying a mutant base call that has indicated that a base at a position in the sample nucleic acid sequence is suspected as being a mutation;

analyzing probe intensities of at least one position that is near the position of the suspected mutation; and

changing the mutant base call to a nonmutant base call if the probe intensities of at least one position that is near the position of the suspected mutation are inconsistent with a mutation.

Regarding claims directed to computer program products, the following claim also issued in United States Patent No. 6,242,180:

8. **A computer program product** that calls unknown bases in a sample nucleic acid sequence, comprising:

computer code that receives a plurality of probe intensities, each probe intensity indicating hybridization affinity between a nucleic acid probe and the sample nucleic acid sequence;

computer code that calls bases of the sample nucleic acid sequence according to the plurality of probe intensities;

computer code that identifies a mutant base call that has indicated that a base at a position in the sample nucleic acid sequence is suspected as being a mutation;

computer code that analyzes probe intensities of at least one position that is near the position of the suspected mutation;

computer code that changes the mutant base call to a nonmutant base call if the probe intensities of at least one position that is near the position of the suspected mutation are inconsistent with a mutation; and

a computer readable medium that stores the computer codes.

Regarding computer systems, the following claim also issued in United States Patent No. 6,242,180:

10. **A computer system**, comprising:

a processor; a computer readable medium coupled to the processor that stores a computer program, the computer program including:

computer code that receives a plurality of probe intensities, each probe intensity indicating hybridization affinity between a nucleic acid probe and the sample nucleic acid sequence;

computer code that calls bases of the sample nucleic acid sequence according to the plurality of probe intensities;

computer code that identifies a mutant base call that has indicated that a base at a position in the sample nucleic acid sequence is suspected as being a mutation;

computer code that analyzes probe intensities of at least one position that is near the position of the suspected mutation;

computer code that changes the mutant base call to a nonmutant base call if the probe intensities of at least one position that is near the position of the suspected mutation are inconsistent with a mutation.

Other examples include, e.g., United States Patent No. 6,223,186, entitled "System and method for a precompiled database for biomolecular sequence information," issued on April 24, 2001:

26. **A computer program product** for a computer system that stores a biomolecular database comprising a computer readable storage medium and a

computer program mechanism embedded therein, the computer program product comprising:

a biomolecular database ...; and

a data retrieval module that includes instructions for:

receiving a request for data associated with a particular attribute of the particular entry of a particular entity and returning the retrieved data to the requester,

determining a particular entity offset value associated with the particular entry of the particular entity, and

retrieving data using the particular entity offset value.

Other examples include, e.g., United States Patent No. 6,125,331, entitled "Structural alignment method making use of a double dynamic programming algorithm," issued on September 26, 2000:

1. **A structural alignment method** for proteins using a double dynamic programming algorithm, the method comprising the steps of:

(a) performing a first distance cut-off approximation for determining a first local environment of a first residue of a first protein centered at a side chain of said first residue of said first protein, and residues with side chain centers that are present within said first distance cut-off are selected as constituent elements of said first local environment of said first residue, wherein a number of residues in said first local environment is less than a number of residues in said first protein;

performing a second distance cut-off approximation for determining a second local environment of a second residue of a second protein centered at a side chain of said second residue of said second protein, and residues with side chain centers that are present within said second distance cut-off are selected as constituent elements of said second local environment of said second residue;

(b) performing .DELTA.N cut-off approximation for selectively comparing residue pairs obtained by said first and second distance cut-off approximations having a first similarity of local environments, said first similarity having a value based on a result of said step of performing .DELTA.N cut-off approximation;

(c) generating a 3-dimensional structural alignment of said first protein with said second protein using results of said first and second distance cut-off approximations and said .DELTA.N cut-off approximation; and

(d) outputting said 3-dimensional structural alignment indicating residue-to-residue correspondence between said first protein and said second protein,

wherein said 3-dimensional structural alignment is generated so that a total sum of values of similarities for pairs of said first and second residues included in said 3-dimensional structural alignment is a maximum.

13. **A computer-implemented system** for structural alignment of proteins using a double dynamic programming algorithm, the system comprising:
means for performing a first distance cut-off approximation ...;
means for performing a second distance cut-off approximation ...;
means for performing .DELTA.N cut-off approximation ...; and
means for generating a 3-dimensional structural alignment...; and
means for outputting said 3-dimensional structural alignment, ... ,
wherein said 3-dimensional structural alignment is generated so that a total sum of values of similarities for pairs of said first and second residues included in said 3-dimensional structural alignment is a maximum.

17. **A computer program product** including a computer readable medium, ..., the method steps comprising:
performing a first distance cut-off approximation...;
performing a second distance cut-off approximation...;
performing .DELTA.N cut-off approximation ...;
generating a 3-dimensional structural alignment ...; and
outputting said 3-dimensional structural alignment ...,
wherein said 3-dimensional structural alignment is generated so that a total sum of values of similarities for pairs of said first and second residues included in said 3-dimensional structural alignment is a maximum.

Accordingly, Applicants respectfully aver that, after entry of the amendment the pending claims, directed to computer program products, computer-implemented methods and computer systems, are statutory subject matter under 35 U.S.C. §101.

Issues under 35 U.S.C. §112, second paragraph

The term "geometric descriptor"

The rejection of claims 1 to 22, and 43-50 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the term "geometric descriptor" is at issue. Please note that the claims do not contain this term.

Issues under 35 U.S.C. §102(b)

Holm, et al.

The rejection of claims 1, 3-10, 12, 15-22, and 43-50 under 35 U.S.C. §102(b) as allegedly being anticipated by Holm, *et al.* (1997) PROTEINS: Structure, Function and Genetics 28:72-82 (hereinafter "Holm") has been maintained for reasons of record, paragraph no. 9 in paper no. 9 is referenced.

The legal standard for anticipation under 35 U.S.C. §102 is one of strict identity. To anticipate a claim, a single prior source must contain each and every limitation of the claimed invention.

Applicants respectfully maintain that Holm does not teach each and every element of Applicants' claimed invention.

Holm purports to report global structural conservation patterns in amidohydrolases related to urease. However, Holm does not identify a subset of geometric constraints that represent only an active site or other functional site of these proteins. Rather, the authors specifically reported that *"[R]esidue-by-residue optimal alignment and superimposition of three-dimensional structures* reveals a common structural core consisting of an ellipsoidal $(\beta\alpha)_8$ barrel with a conserved metal binding site at the C-terminal end of strands β_1, β_5, β_6, and β_8" (Holm, page 72, right-hand column, emphasis added).

This claimed invention does not include a residue-by-residue optimal alignment followed by a superimposition of three-dimensional structures. In contrast, after entry of the instant amendment, the claimed invention is directed to computer implemented methods, computer program products and computer systems encoding at least one functional site descriptor of a protein (other than a divalent metal ion binding site), the functional site descriptor comprising an amino acid residue identity constraint for at least one amino acid residue of the functional site, wherein the amino acid residue is identified as a single amino residue or as a subset of amino acid residues; and, one or more geometric constraints between at least three different atoms, wherein each atom is in a different amino acid residue of the protein and the different atoms comprise (i) an atom of a first amino acid residue of the functional site comprising the amino acid residue of part (a), wherein the atom is selected from the group

consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, a backbone pseudoatom and a beta-carbon; (ii) an atom of a second amino acid residue of the functional site, wherein the atom is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, a backbone pseudoatom and a heta-carbon; and, (iii) an atom of a third amino acid residue of the protein, wherein the atom is selected from the group consisting of a backbone atom, a side chain atom and a pseudoatom. Holm does not teach or suggest all of thesc limitations.

According, because Holm fails to teach or suggest, explicitly or inherently, each and every element of Applicants' claimed invention, it is not anticipatory. Accordingly, the rejection under 35 U.S.C. §102 should be withdrawn.

Issues under 35 U.S.C. §103(a)

Wallace, et al.

The rejection of claims 1 to 22 and 43 to 52 under 35 U.S.C. §103(a) as allegedly being unpatentable over Wallace, *et al.* (1996) Protein Science 5:1001-1013 (hereinafter "Wallace") has been maintained for reasons of record; paragraph no. 12 in paper no. 9 is referenced.

In the instant office action, the Patent Office alleges that the pending claims are not limited to reprcsentation by "non-catalytic backbone" atoms, while Applicants argue that nothing in Wallace suggests that a functional site descriptor can be represented by "non-catalytic backbone" atoms, and, that Wallace does not suggest that a functional site descriptor incorporates one or more non-functional backbone atoms.

After entry of the instant amendment, the claimed invention is clearly drawn to computer program products and computer implemented methods encoding at least one functional site descriptor comprising at lcast one non-catalytic backbone atom. Applicants respectfully contend that the following claim languagc obviates this issue:

(b) one or more geometric constraints between at least three different atoms, wherein each atom is in a different amino acid residue of the protein and the different atoms comprise: (i) an atom of a first amino acid residue of the functional site comprising the amino

acid residue of part (a), wherein the atom is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, a backbone pseudoatom and a beta-carbon; (ii) an atom of a second amino acid residue of the functional site, wherein the atom is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, a backbone pseudoatom and a beta-carbon.

Wallace would not have motivated one of ordinary skill in the art to make a functional site descriptor incorporating one or more non-catalytic backbone atoms. Indeed, Wallace's reliance on inclusion of catalytically functional atoms teaches away from Applicants' invention. Accordingly, Applicants respectfully submit that the claimed invention is not obvious over Wallace within the meaning of 35 U.S.C. §103 and the rejection should be withdrawn.

CONCLUSION

In view of the foregoing amendment and remarks, it is believed that the Examiner should withdraw the rejection of the pending claims under 35 U.S.C. §101, 35 U.S.C. §112, second paragraph, 35 U.S.C. §102(b) and 35 U.S.C. §103(a). Applicants believe all claims pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (858) 678-5070.

Respectfully submitted,

Date: July 12, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Applicant : Skolnick et al.
Serial No. : 09/322,067
Filed : May 27, 1999
Title : METHODS AND SYSTEMS FOR PREDICTING PROTEIN FUNCTION

Art Unit : 1631
Examiner : Dr. Michael Borin

In The Claims:

Claims 1, 15, 21, 23 to 43 have been canceled, without prejudice.

Claim 2 has been amended as follows:

2. (Amended) The computer program product of [A functional site descriptor according to] claim 53 [1], wherein the subset of amino acid residues comprising the amino acid identity constraint of step (a) comprises 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acid residues [comprising the functional site are identified as particular amino acid residues] or sets of amino acid residues.

Claim 3 has been amended as follows:

3. (Amended) The computer program product of [A functional site descriptor according to] claim 53 [1], wherein the identity of an amino acid residue specified in the functional site descriptor is selected from the group consisting of Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr and Val.

Claim 4 has been amended as follows:

4. (Amended) The computer program product of [A functional site descriptor according to] claim 53 [1], wherein the identity of an amino acid residue specified in the functional site descriptor comprises a set of two or more amino acid residue identities, wherein each of said amino acid residue identities is selected from the group consisting of Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr and Val.

Claim 5 has been amended as follows:

5. (Amended) The computer program product of [A functional site descriptor according to] claim 53 [1], wherein each geometric constraint within the set of geometric constraints is selected from the group consisting of an atomic position specified by a set of three dimensional coordinates, an interatomic distance, and an interatomic bond angle.

Claim 6 has been amended as follows:

6. (Twice amended) The computer program product of [A functional site descriptor according to] claim 5, wherein at least one member of the set of geometric constraints is an atomic position specified by a set of three dimensional coordinates, wherein the atomic position can vary within a preselected root mean square deviation.

Claim 7 has been amended as follows:

7. (Twice amended) The computer program product of [A functional site descriptor according to] claim 6, wherein the atomic position varies within [an] a root mean square deviation of less than about 3 Å.

Claim 8 has been amended as follows:

8. (Amended) The computer program product of [A functional site descriptor according to] claim 5, wherein at least one member of the set of geometric constraints is an interatomic distance.

Claim 9 has been amended as follows:

9. (Amended) The computer program product of [A functional site descriptor according to] claim 5, wherein at least one member of the set of geometric constraints is an interatomic bond angle range.

Claim 10 has been amended as follows:

10. (Amended) The computer program product of [A functional site descriptor according to] claim 53 [1], further comprising a conformational constraint.

Claim 11 has been amended as follows:

11. (Amended) The computer program product of [A functional site descriptor according to] claim 53 [1], wherein the one or more [that comprises a set of] geometric constraints of step (b) [with respect to] comprises at least one atom from each of 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acid residues that comprise the functional site [corresponding to the functional site descriptor].

Claim 12 has been amended as follows:

12. (Amended) The computer program product of [A functional site descriptor according to] claim 53 [1], whercin all of the atoms for which geometric constraints are provided comprise a part of the protein [polypeptide] backbone and are selected from the group consisting of an α-carbon [α-carbons], an amide nitrogen [nitrogens], a carbonyl carbon [carbons,] and a carbonyl oxygen [oxygens].

Claim 13 has been amended as follows:

13. (Amended) The computer program product of [A functional site descriptor according to] claim 53 [1], wherein at least one of said one or more atoms is a pseudoatom.

Claim 14 has been amended as follows:

14. (Amended) The computer program product of [A functional site descriptor according to] claim 13, wherein the pseudoatom is a center of mass with respect to at least two atoms selected from the group consisting of an atom [atoms] from one amino acid residue and an atom [atoms] from at least two amino acid residues of the protein.

Claim 16 has been amended as follows:

16. (Amended) The computer program product of [A functional site descriptor according to] claim 53 [1], wherein the functional site descriptor defines a functional site of a protein comprising [for a] biological function selected from the group consisting of a disulfide oxidoreductase activity, a α/β hydrolase activity, a phospholipase activity, and a T1 ribonuclease activity.

Claim 17 has been amended as follows:

17. (Amended) The computer program product of [A functional site descriptor according to] claim 53 [1], wherein the functional site descriptor is selected from the group consisting of a three atom functional site descriptor, a four atom functional site descriptor, a five atom functional site descriptor, a six atom functional site descriptor, a seven atom functional site descriptor, an eight atom functional site descriptor, a nine atom functional site descriptor, a ten atom functional site descriptor, an eleven atom functional site descriptor, a twelve atom functional site descriptor, a thirteen atom functional site descriptor, a fourteen atom functional site descriptor, and a fifteen atom functional site descriptor.

Claim 18 has been amended as follows:

18. (Amended) The computer program product of [A functional site descriptor according to] claim 53 [1], wherein the functional site descriptor is selected from the group consisting of an active site of an enzyme, a ligand binding domain, and a protein-protein interaction domain.

Claim 19 has been amended as follows:

19. (Amended) The computer program product of [A functional site descriptor according to] claim 18, wherein ligand binding domain binds a ligand selected from the group consisting of a substrate, a co-factor, and an antigen.

Claim 20 has been amended as follows:

20. (Amended) The computer program product of claim 53, [A library of functional site descriptors], wherein the computer program product encodes a library [comprises at least one] of functional site descriptors [descriptor according to claim 1].

Claim 22 has been amended as follows:

22. (Amended) The computer program product of [A library of functional site descriptors according to] claim 20, wherein the library comprises at least two functional site descriptors for at least one of the biological functions represented by the library.

Claim 44 has been amended as follows:

44. (Amended) The [A] method [according to] of claim 54 [43], wherein the functional site descriptor is selected from the group consisting of an active site of an enzyme, a ligand binding domain, and a protein-protein interaction site.

Claim 45 has been amended as follows:

45. (Amended) A computer program product comprising a computer useable medium having computer program logic recorded thereon for creating a functional site descriptor for use in predicting a biological function of a protein, said computer program logic comprising computer program code logic configured to perform the operations of:

(a) determining a set of geometric constraints for a functional site associated with a biological function of a protein, wherein a set of geometric constraints comprises one or more geometric constraints between at least three different atoms, wherein each atom is in a different amino acid residue of the protein and the different atoms comprise:

(i) an atom of a first amino acid residue of the functional site comprising the amino acid residue of part (a), wherein the atom is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, a backbone pseudoatom and a beta-carbon;

(ii) an atom of a second amino acid residue of the functional site, wherein the atom is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, a backbone pseudoatom and a beta-carbon; and,

(iii) an atom of a third amino acid residue of the protein, wherein the atom is selected from the group consisting of a backbone atom, a side chain atom and a pseudoatom,

(b) modifying one or more geometric constraints of said set of geometric constraints to produce a modified set of geometric constraints,

(c) comparing said modified set of geometric constraints to a data set of functional sites correlated with said biological function to determine whether said modified set of geometric constraints compares [favorably] positively with said data set of functional sites correlated with said biological function and, if [so] there is a positive correlation:

(d) repeating said modifying and comparing operations of steps b and c to modify one or more of said geometric constraints of said set of geometric constraints to an extent that said modified set of geometric constraints compares [favorably] positively with said data set of functional sites correlated with said biological function without encompassing a predetermined amount of data sets not correlated with said biological function.

Claim 46 has been amended as follows:

46. (Amended) The [A] computer program product of [according to] claim 45, wherein said operation of determining a set of geometric constraints of a

functional site correlated with a biological function of a protein comprises recciving said set of geometric constraints from at least one group of a data set of predetermined geometric constraints or from a user input.

Claim 47 has been amended as follows:

(Amcnded) The [A] computer program product of [according to] claim 45, whcrein said set of geometric constraints concerns one or more atoms in each of two or more amino acid residues comprising a functional site of a protein, wherein at least one of said two or more amino acid residues is identified as a particular amino acid residue or set of amino acid residues,

wherein said one or more atoms is selected from the group consisting of a backbone amide nitrogen [nitrogens], an alpha-carbon [alpha-carbons], a backbone carbonyl carbon [carbons, and], a backbone carbonyl oxygen [oxygens within a polypeptide backbone], beta-carbons of amino acid residues, and pseudoatoms[, and wherein at least one of said one or more atoms is an amide nitrogen, an alpha-carbon, a bcta-carbon, or a beta-carbon within a polypeptide background].

Claim 48 has been amended as follows:

48. (Amendcd) The [A] computer program product of [according to] claim 45, wherein said set of geometric constraints further comprises one or more geometric constraints with respect to one or more atoms or pseudoatoms of one or more amino acid residues that arc adjacent to an amino acid residue of said two or more amino acid residues.

Claim 49 has been amended as follows:

49. (Amended) The [A] computer program product of [according to] claim 45, wherein said set of geometric constraints comprises geometric constraints selected from the group consisting of atomic positions specified by sets of three dimensional coordinates, interatomic distances, and interatomic bond angles.

Claim 50 has been amended as follows:

50. (Amended) The [A] computer program product of [according to] claim 45, wherein at least one of the geometric constraints of said set of geometric constraints comprises interatomic distances between one or more atoms and/or pseudoatoms of the amino acid residues of the functional site descriptor.

Claim 51 has been amended as follows:

51. (Amended) The [A] computer program product of [according to] claim 45, wherein said operation of modifying one or more geometric constraints of said set of geometric constraints to produce a modified set of geometric constraints comprises associating a predetermined variance with one or more of the geometric constraints.

Claim 52 has been amended as follows:

52. (Amended) The [A] computer program product of [according to] claim 45, wherein said operation of modifying one or more geometric constraints of said set of geometric constraints to produce a modified set of geometric constraints comprises:

computing an average value for a geometric constraint within the set of geometric constraints by determining values for said geometric constraint from two different proteins having functional sites that correlate with said biological function, and calculating said average value;

computing a standard deviation with respect to such geometric constraint; and

applying a multiplier to said computed standard deviation to generate said modified geometric constraint [geometry].

The following new claims have been added:

--53. A computer program product encoding a functional site descriptor, wherein the functional site descriptor defines at least one functional site of a protein, other than a divalent metal ion binding site, the functional site descriptor comprising:

(a) an amino acid residue identity constraint for a first amino acid residue of the functional site, wherein the first amino acid residue is identified as a single amino residue or as a subset of amino acid residues; and,

(b) one or more geometric constraints between at least three different atoms, wherein each atom is in a different amino acid residue of the protein and the different atoms comprise:

(i) an atom of the first amino acid residue of the functional site, wherein the atom is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, a backbone pseudoatom and a beta-carbon;

(ii) an atom of a second amino acid residue of the functional site, wherein the atom is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, a backbone pseudoatom and a beta-carbon; and,

(iii) an atom of a third amino acid residue of the protein, wherein the atom is selected from the group consisting of a backbone atom, a side chain atom and a pseudoatom.

54. A computer implemented method for determining a functional site descriptor that defines a spatial configuration of a functional site, wherein the functional site descriptor defines a functional site of a protein other than a divalent metal ion binding site, the method comprising the following steps:

(a) identifying an amino acid residue identity constraint for a first amino acid residue of the functional site, wherein the first amino acid residue is identified as a single amino residue or as a subset of amino acid residues; and,

(b) identifying one or more geometric constraints between at least three different atoms, wherein each atom is in a different amino acid residue of the protein and the different atoms comprise:

(i) an atom of the first amino acid residue of the functional site, wherein the atom is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, a backbone pseudoatom and a beta-carbon;

(ii) an atom of a second amino acid residue of the functional site, wherein the atom is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, a backbone pseudoatom and a beta-carbon; and,

(iii) an atom of a third amino acid residue of the protein, wherein the atom is selected from the group consisting of a backbone atom, a side chain atom and a pseudoatom,

thereby determining a functional site descriptor.

55. The method of claim 54, wherein the spatial configuration of the protein functional site corresponds to at least one biological function.

56. A computer-implemented method for defining a functional site descriptor of a protein comprising the following steps:

(a) identifying an amino acid residue identity constraint for a first amino acid residue of the functional site, wherein the first amino acid residue is identified as a single amino residue or as a subset of amino acid residues; and,

(b) identifying one or more geometric constraints between at least three different atoms, wherein each atom is in a different amino acid residue of the protein and the different atoms comprise:

(i) an atom of the first amino acid residue of the functional site, wherein the atom is selected from the group consisting of a backbone amide nitrogen, an

alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, a backbone pscudoatom and a beta-carbon;

(ii) an atom of a second amino acid residue of the functional site, wherein the atom is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, a backbone pseudoatom and a beta-carbon; and,

(iii) an atom of a third amino acid residue of the protein, wherein the atom is selected from the group consisting of a backbone atom, a side chain atom and a pseudoatom, thereby determining a functional site descriptor.

57. A computer program product for defining a functional site descriptor of a protein comprising a computer useable medium comprising a computer readable program code embodied therein, wherein the computer program product is capable of defining a functional site descriptor of a protein by a process comprising the following steps:

(a) identifying an amino acid residue identity constraint for a first amino acid residue of the functional site, wherein the first amino acid residue is identified as a single amino residue or as a subset of amino acid residues; and,

(b) identifying one or more geometric constraints between at least three different atoms, wherein each atom is in a different amino acid residue of the protein and the different atoms comprise:

(i) an atom of the first amino acid residue of the functional site, wherein the atom is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, a backbone pseudoatom and a beta-carbon;

(ii) an atom of a second amino acid residue of the functional site, wherein the atom is selected from the group consisting of a backbone amide nitrogen, an alpha-carbon, a backbone carbonyl carbon, a backbone carbonyl oxygen, a backbone pscudoatom and a beta-carbon; and,

(iii) an atom of a third amino acid residue of the protein, wherein the atom is selected from the group consisting of a backbone atom, a side chain atom and a pseudoatom, thereby determining a functional site descriptor.

58. A computer system, comprising:

(a) a processor; and

(b) a computer program product as set forth in claim 45.

59. A computer system, comprising:

(a) a processor; and

a computer program product as set forth in claim 53.

60. A computer system, comprising:

(a) a processor; and

(c) a computer program product as set forth in claim 57.--